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## CASE STUDY

# Muscle synergies after stroke are correlated with perilesional high gamma

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## Abstract

Movements can be factored into modules termed “muscle synergies”. After stroke, abnormal synergies are linked to impaired movements; however, their neural basis is not understood. In a single subject, we examined how electrocorticography signals from the perilesional cortex were associated with synergies. The measured synergies contained a mix of both normal and abnormal patterns and were remarkably similar to those described in past work. Interestingly, we found that both normal and abnormal synergies were correlated with perilesional high gamma. Given the link between high gamma and cortical spiking, our results suggest that perilesional spiking may organize synergies after stroke.

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## Introduction

The motor system faces a daunting task of controlling a very large number of motor parameters. However, because multiple muscles are recruited in a concerted manner, their coordinated activity appears to be organized into a reduced set of muscle primitives or “muscle synergies,” possibly offering a predictable strategy for movement control.<sup>1–3</sup> These synergies can be measured by creating lower dimensional representations of electromyography (EMG) signals. After stroke, however, there is a distinct change in the modular recruitment of muscles, thus resulting in abnormal synergies in the most impaired subjects.<sup>4–6</sup> While the neural basis of such abnormal synergies is poorly understood, a commonly held view is that descending cortical inputs can shape subcortical circuits to organize and dynamically control the weighting of synergies.<sup>7</sup> However, it is unclear how perilesional cortical activity might be related to both the normal and abnormal muscle synergies observed after stroke. In a unique subject with stroke-related cortical injury and abnormal movements, we recorded subdural electrocorticography (ECoG) signals using high-density arrays localized to the perilesional cortex while also simultaneously recording EMG from the affected arm during reaching movements. We aimed to specifically test the hypothesis that perilesional cortical activity is correlated with the activations of post-stroke muscle synergies.

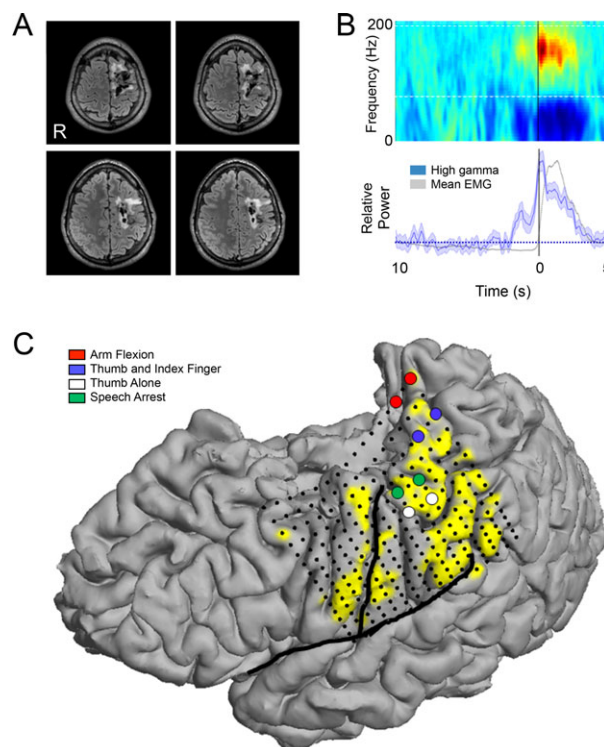
## Materials and Methods

### Subject

A 35-year-old right-handed man with a left hemisphere stroke underwent intracranial monitoring for refractory epilepsy (Fig. 1). Electrode placement was solely determined on clinical grounds. No cognitive deficits were detected and antiepileptic drug therapy was discontinued during recordings. The patient consented to participate and the study protocol was approved by the UCSF CHR.

### Electrophysiology

A 256-channel ECoG grid with platinum–iridium electrodes (2 mm diameter) was used; signals were amplified via a preamplifier (TDT; Tucker-Davies Technologies, Alachua, FL) and digitized at 1017 Hz.<sup>8</sup> An Ojemann stimulator (1–3.5 mA, 60 Hz, 1 msec) was used for mapping a 64-electrode subset. A stimulation response was assessed by testing three randomized times and observing for the same response (Fig. 1C). EMG signals were

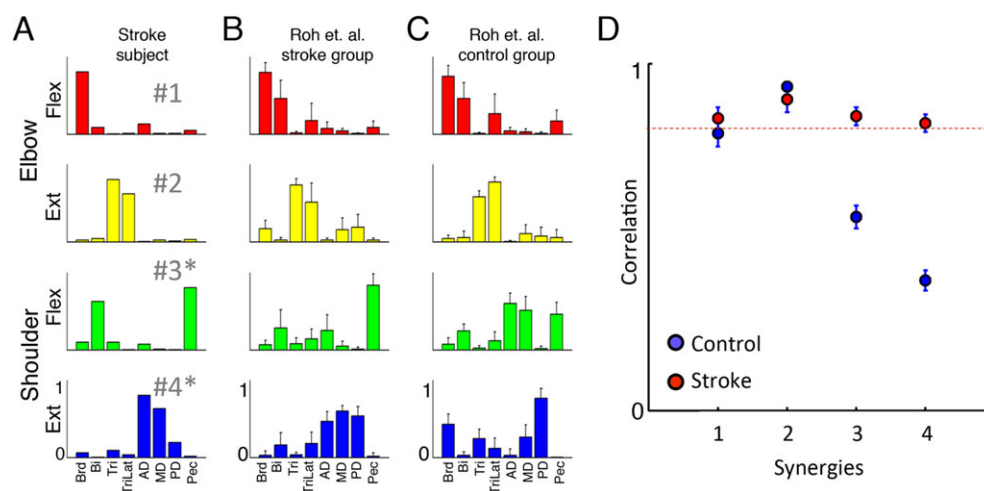


**Figure 1.** ECoG grid placement and cortical activity in a subject with history of a stroke. (A) FLAIR MRI showing stroke in the left hemisphere. (B) Time-power characteristics of a single electrode averaged across trials. Upper panel represents the mean spectral power over time (time 0 is onset EMG). Dashed white lines indicate high gamma band power (76–200 Hz). Lower panel shows the time-power plot of high gamma activity (with SEM) and mean EMG. (C) Three-dimensional reconstruction of MRI-CT co-registration and ECoG electrode grid placement. Color-coded dots indicate the pattern observed during intraoperative mapping with electrical stimulation. Areas of significant pre-movement high gamma activity indicated in yellow. Upper vertical dark line marks the central sulcus. Lower line denotes the Sylvian Fissure. ECoG, electrocorticography; MRI, magnetic resonance imaging; EMG, electromyography.

recorded from eight muscles: brachioradialis (BRD); biceps brachii (BI); triceps brachii, long and lateral heads (TRl long and TRl lat, respectively); deltoid, anterior, medial, and posterior fibers (AD, MD, and PD, respectively); pectoralis major (clavicular fibers; PECTclav).

### Behavioral task

The task consisted of reaching movements in the horizontal plane from a center to one of four targets. Each trial started with the subject's hand at the center. After a 1500–4000 msec delay, the target changed color indicating “Go.” Sixteen reaches were made to each target. Positions were tracked with a video camera (i.e. markers on shoulder, elbow, hand).



**Figure 2.** Muscle synergies using negative matrix factorization (NMF). (A) Pattern of muscle synergies in our subject using NMF. (B) Reproduction of average muscle synergies in 10 stroke subjects from Roh et al.<sup>6</sup> (C) Reproduction of average muscle synergies in 12 control subjects from Roh et al.<sup>6</sup> (D) Correlation of each of our subjects' synergies with the control and stroke muscle synergies shown in (B and C) (whiskers show SEM, dashed red line indicates bootstrap significance). \* in (A) denotes an abnormal synergy.

## Analysis

ECoG signals were band-pass filtered and down-sampled to 400 Hz. Electrodes with movement-related activity were identified using a two-tailed *t*-test of segments before and after movement. A 80-point tapered root mean square (RMS) filter was applied to the EMG to rectify prior to downsampling (400 Hz). Data from  $-5$  to  $+4$  seconds relative to movement onset were used for analysis. Nonnegative matrix factorization (NMF) was used to calculate synergies.<sup>6</sup> NMF was performed using the MATLAB function, Natick, Massachusetts, U.S.A with 100 replicates to repeat the factorization using random starting values, to produce five weights, the minimum for synergies to have a  $>90\%$  "variance accounted for." We compared the cross-correlation coefficient (CC) of ECoG relative to the muscle synergy across time-shifts ("lags"); ECoG activity in each frequency band and synergy activation time-series were correlated as a function of the temporal lag using the Matlab function *xcorr*. Each electrode's CC was normalized using the CC values from "baseline" electrodes that contained activity not significantly related to the temporal course of synergy activation (see Data S1). Finally, we quantified the similarity between the sets of synergies in our subject with that of a cohort of control and stroke patients from a recently published paper<sup>6</sup>; we calculated an inner product column similarity measure using the *matcorr* function. Bootstrapping was then used to determine the chance level of similarity (Data S1).<sup>6</sup>

## Results

Intracranial recordings were conducted in a stroke subject who suffered from refractory seizures and weakness in both the distal and the proximal affected arm, with an upper-extremity Fugl-Meyer score of 35. The stroke involved frontal, premotor and motor areas of the left hemisphere (Fig. 1A). Unlike a typical patient without brain injury, intraoperative mapping revealed that movements of the affected limb could be easily elicited via electrodes posterior to the central sulcus (Fig. 1C). Such an abnormal pattern may represent post-stroke reorganization of the motor map. Reaction time from the "Go" cue to movement onset (i.e. rise in mean EMG activity) was significantly slower for the affected versus unaffected arm (mean reaction time of  $635 \pm 40$  and  $365 \pm 18$  msec, respectively,  $P < 0.001$ , unpaired *t*-test). The reach time from movement onset to target acquisition was significantly longer for the affected arm (mean reach time of  $1266 \pm 58$  msec vs.  $856 \pm 26$  msec,  $P < 0.001$ , unpaired *t*-test).

To quantify the cortical correlates of movement, we transformed each electrode's recorded signal into their component frequencies and power across time (aligning on the rise of EMG activity for trial averaging) (Fig. 1B). There was both a movement-related reduction in low-frequency power and an increase in high-gamma (i.e. 76–200 Hz) power. In a subset of electrodes, high-gamma activity preceded movement onset (Fig. 1B, bottom panel). The yellow shading shown in Figure 1C represents electrodes that demonstrated significant movement-related

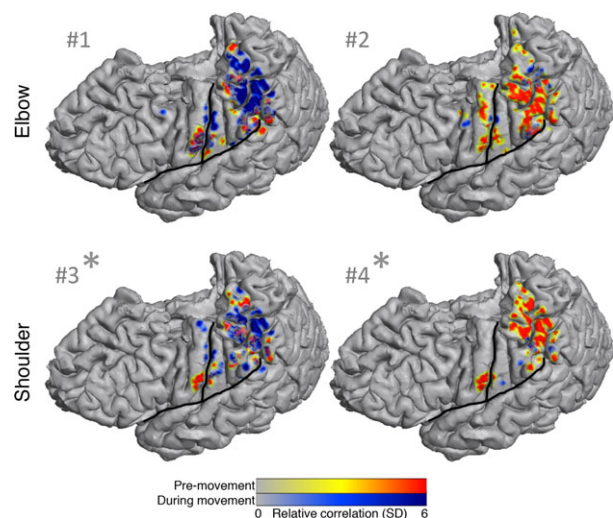
high gamma activity. Interestingly, the majority of the movement-related activity was anatomically centered posterior to the central sulcus and in the inferior parietal cortices. While there is certainly expected to be individual variation in the patterns of cortical activation, this subject's pattern of activations appears to be distinct from that frequently seen in intact subjects.<sup>9,10</sup> Together with the results of the intraoperative mapping, it appeared that the poststroke cortical control of movements was reorganized to regions posterior to the central sulcus.

Dimensionality reduction techniques were employed on EMG activity from 8 arm muscles to elucidate how stroke damage affected co-activation patterns of muscle groups (Fig. 2A). Four of the five muscle synergies from our subject were remarkably similar to recently published muscle synergies from the affected and the unaffected upper arm of stroke patients (Fig. 2B and C reproduced from Roh et al.,<sup>6</sup> see Fig. S1 for synergy 5). While our subject's elbow-related synergies were not significantly different from the controls in the Roh et al. study,<sup>6</sup> the shoulder-related synergies showed abnormal co-activation that was most consistent with synergies from the stroke group (Fig. 2D). We thus categorized synergies #1 and #2 as "normal", and synergies #3 and #4 as "abnormal".

We next examined the relationship between high-gamma cortical activity and the calculated muscle synergies. We specifically examined the spatial and temporal dynamics with which the muscle synergies co-varied with

high-gamma ECoG signals across the array. We calculated the cross-correlation value between the ECoG gamma band activity and individual muscle synergy activation profiles. More specifically, the cross-correlation values measured the similarity of the two signals across multiple time shifts of the ECoG signal relative to the muscle synergies. This analysis also provided information about the specific temporal lag between the ECoG activity and the activation of the synergies. For synergy #1, which was strongly weighted by the brachioradialis, and #3, representing a pectoral and biceps synergy, there was a positive lag (respectively,  $156 \pm 42$  and  $44 \pm 29$  msec, mean  $\pm$  SEM). In contrast, synergy #2, weighted by the triceps group, and synergy #4, i.e. the "deltoid group", had a negative lag with respect to the ECoG signal (respectively,  $-437 \pm 50$  and  $-228 \pm 34$  msec). When these correlations were spatially mapped onto the magnetic resonance imaging of the subject's brain, they produced distinct spatiotemporal patterns of cortical activity for each synergy (Fig. 3). Interestingly, while synergies #2 and #4, which were weighted by muscles that have a predominant extensor action, had strong pre-movement correlation, the synergies linked to muscles with a predominant flexion action were linked to activity that was mostly after onset. This suggests that the cortical dynamics may be distinct for different functional groups.

Moreover, we also contrasted the size of the cortical representations (i.e. the number of electrodes) for the respective sets of normal and abnormal synergies (i.e. comparison of #1 vs. #3/#4 and #2 vs. #1/#4 shown in Fig. S2). Importantly, we found that in both cases more electrodes were correlated with the timecourse of the normal as opposed to the abnormal synergy (#1 vs. #3: 44% vs. 36%; #1 vs. #4: 44% vs. 25%; #2 vs. #3: 44% vs. 36%; #2 vs. #4: 44% vs. 25%;  $P < 0.01$  paired  $t$ -test for all comparisons). Thus, for all comparisons, there were more electrodes correlated with normal versus the abnormal synergies. We also tested and did not find any evidence for significant correlation with other frequency bands (i.e.  $\delta = 1-4$  Hz,  $\theta = 4-8$  Hz,  $\alpha = 8-12$  Hz,  $\beta = 18-26$  Hz, low  $\gamma = 30-50$  Hz<sup>11-13</sup>).



**Figure 3.** Spatiotemporal patterns of cortical activity linked to muscle synergies. Electroencephalography (ECoG)-muscle synergy cross-correlation map indicating electrodes with highest correlation of ECoG activity occurring before synergy activity (yellow and red) and ECoG activity occurring after synergy onset (blue). Amplitude of correlation is depicted by the intensity of the electrode's respective color (see color bar below). The indicated number (i.e. #1-4) corresponds to synergies in Figure 2. \*An abnormal synergy.

## Discussion

Our subject's stroke induced widespread injury to motor circuits with resulting impaired movements and disability. Detailed monitoring of movements as well as EMG revealed that our subject had a commonly seen pattern of both normal and abnormal muscle synergies,<sup>6</sup> thus providing a unique case to conduct detailed analysis of how cortical activity is linked to movement control after stroke. After several years poststroke and in the presence of abnormal movements, we found evidence for



perilesional cortical high gamma activations associated with movements. Our patient's pattern of movement-related posterior cortical high gamma activation are much greater in comparison to the recruitment of cortical regions frequently seen in subjects without cortical injury.<sup>9,10</sup> Both the stimulation mapping and the movement-related ECoG activity suggest that postcentral areas underwent reorganization to partially restore volitional control over elbow and shoulder muscles.

One primary goal of this study was to examine the link between perilesional activity, as measured using high-resolution micro-ECoG, and the activation of muscle synergies after stroke. Moreover, because our subject's movements resulted in two normal and two abnormal synergies, we could further analyze how perilesional cortical activations were linked to the various muscle synergy groups after stroke. We found that perilesional high-gamma oscillations were significantly correlated with both the normal and abnormal synergies. In contrast, no other frequency band was correlated with the activation profiles. What does the relationship with perilesional high-gamma indicate? There is a growing body of literature supporting the notion that ECoG high-gamma activity is a proxy for synchronized local neural spiking activity at the cortical surface.<sup>14,15</sup> Thus our results suggest that perilesional cortical spiking activity may be significantly correlated with both abnormal and normal synergies after stroke. This is also consistent with the literature suggesting that cortical activity is correlated with muscle synergies in intact animals.<sup>1–3</sup> Our results further suggest that top down modulation from perilesional cortex may organize the poststroke muscle synergies. Future studies aimed at modulating perilesional spiking activity could determine a more causal and functional role in shaping both normal and abnormal muscle synergies.

Our subject had both normal and abnormal synergies several years poststroke. His pattern was very similar to a recently studied cohort of stroke subjects, where newly formed abnormal synergies were also observed.<sup>6</sup> However, another study found that synergies in the affected arm of severely impaired patients could be derived by merging and fractionation of synergies calculated in the unaffected upper-limb, that is, new synergies were not evident.<sup>5</sup> A possible reason for differences may be the neuroanatomical site of the lesion; stroke subjects with intact sensorimotor cortex have been found to have less similar synergies relative to the unaffected limb.<sup>16</sup> Thus, it is possible that intact cortical structures may trigger the formation of abnormal synergies. In this subject, our finding of significant cortical activity linked to the various synergies suggests that the posterior parietal region may also give rise to new synergies. It is important to note, however, that a significant

limitation of this study is that awake-motor mapping using transcranial magnetic stimulation (TMS) was not conducted. Past studies have indicated that this can localize the cortical sites of synergies.<sup>17</sup>

Finally, there were remarkable similarities between the spatiotemporal and regional activation of cortical areas for both the normal and the abnormal synergies. We did, however, find that the number of ECoG electrodes correlated with the activation of normal synergies was greater than that for abnormal synergies. Given that we used an ECoG grid, this suggests that the area of cortical tissue devoted to each synergy after physiological reorganization of the perilesional and surrounding cortical tissue<sup>18–20</sup> after stroke may also be an important variable for physiological reorganization that leads to normal synergies after stroke. Future studies in larger cohorts of subjects with stroke can help determine the precise role of the size of the cortical representation and associated spiking in organizing and shaping muscle synergies after stroke.

## Acknowledgments

We thank Jinsook Roh for providing the weight values used to make Figure 2B and C.<sup>6</sup>

## Author Contributions

E. C. performed all surgical procedures. T. G., E. C., and K. G. conceived of the experiments and collected the data. J. G. and T. G. analyzed the data. B. D. contributed materials for analysis. J. G. and K. G. wrote the manuscript. T. G. and E. C. edited the manuscript.

## Conflict of Interest

None.

## Data and Materials Availability

We will make the MATLAB code available upon request.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Data S1.** Supplemental methods.

**Figure S1.** Weights for synergy #5.

**Figure S2.** Difference maps. Differences in activation area between corresponding normal and abnormal synergies. Yellow color is used to indicate areas that were present in the normal, but not the abnormal synergy map. Blue represents the opposite relationship. The fact that all difference maps contain more yellow than blue suggests that the normal synergies had a larger cortical representation. As also outlined in the results section, there were more electrodes correlated with normal activations in comparison to the abnormal activations (“Normal” mean = 44% of electrodes; “Abnormal” mean = 30.5 of electrodes,  $P < 0.01$ , paired  $t$ -test).